［課程－２］

審査の結果の要旨

氏名 鐘　丞

Tubulin belongs to protein superfamily of globular proteins. Monomer tubulin can polymerize into microtubules, which are highly dynamic and play a critical role in mitosis during cell division. Therefore, microtubule dynamics is an important target for the developing anti-cancer drugs. Inhibition of tubulin polymerization or depolymerization has been utilized and shown efficacy in many types of solid tumors. A novel small molecule PTC596 directly binds tubulin and inhibits microtubule polymerization and has been shown to downregulates MCL-1 and induces p53-independent apoptosis in acute myeloid leukemia cells. I herein investigated the efficacy of another novel microtubule polymerization inhibitor and obtained the following results.

PTC-028 induced growth suppression and apoptosis of MDS cell lines. The efficacy of PTC-028 in primary MDS samples was also confirmed by cell proliferation assays. PTC-028 synergized with hypomethylating agents, such as decitabine and azacitidine, to inhibit the growth and induce apoptosis of MDS cells. Mechanistically, a treatment with PTC-028 induced G2/M arrest followed by apoptotic cell death. Finally, I assessed the efficacy of PTC-028 in a xenograft mouse model of MDS using an MDS cell line, MDS-L and AkaBLI bioluminescence imaging system system, which is composed of AkaLumine-HCl and Akaluc. PTC-028 prolonged the survival of mice in xenograft models.

In summary, my data reveal a possible chemotherapeutic strategy for MDS by disruption of microtubule dynamics as a single agent and in combination with hypomethylating agents. My research suggests a novel therapeutic strategy for MDS.

よって本論文は博士（ 医　学 ）の学位請求論文として合格と認められる。